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PALMER & DODGE, LLP			EXAMINER	
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111 HUNTINGTON AVENUE			ART UNIT	PAPER NUMBER
BOSTON, MA 02199				1632

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/884,384	ZOGHBI ET AL.
	Examiner Anne-Marie Falk, Ph.D.	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 06 August 2003.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

4) Claim(s) 1,3-11,13-15,17,18 and 20-25 is/are pending in the application.

4a) Of the above claim(s) 4,5,7-11,13-15,17,18,20,22 and 23 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1,3,6,21,24 and 25 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 19 June 2001 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) All b) Some \* c) None of:  
1. Certified copies of the priority documents have been received.  
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)      4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.  
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)      5) Notice of Informal Patent Application (PTO-152)  
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 0902.      6) Other: \_\_\_\_\_

## DETAILED ACTION

The preliminary amendment filed June 19, 2001 has been entered. Claim 2 was cancelled.

Claims 11-24 were newly added.

The amendment filed March 18, 2003 (Paper No. 7) has been entered. Claims 1 and 3 have been amended. Claims 12, 16, and 19 have been cancelled. Claim 25 has been newly added.

Accordingly, Claims 1, 3-11, 13-15, 17, 18, and 20-25 are pending in the instant application.

Applicants' election with traverse of Group I, Claims 1 and 3, in Paper No. 7 is acknowledged. The elected invention is drawn to a method of treating a neurodegenerative disease in a mammal by administering a chaperone or chaperone-like compound. Applicants request that Groups IV and IX be rejoined with Group I because Applicants assert that the subject matter of the claims in Groups I, IV, and IX is not distinct. Applicants argue that the two methods in Groups I and IV are not capable of separate practice because one of skill in the art practicing the method of the invention of Group I (treating a neurodegenerative disease by administering a chaperone or chaperone-like compound) would also be practicing the method of the invention of Group IV (treating a neurodegenerative disease by administering a compound that increases the concentration of a chaperone in the neurological system). Likewise, Applicants argue that there is overlap between the scope of Groups I and IX. Applicants' arguments with regard to the overlap are persuasive and Claims 6, 21, 24, and 25 have been rejoined to Group I.

With the exception of the rejoinder of Groups IV and IX with Group I, the remaining restriction requirement is still deemed proper and is therefore made FINAL.

Claims 4, 5, 7-11, 13-15, 17, 18, 20, 22, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicants timely traversed the restriction requirement in Paper No. 7.

Newly added Claim 25 falls into Group IX of the restriction requirement set forth in the Office Action mailed 12/17/02.

Accordingly, Claims 1, 3, 6, 21, 24, and 25 are examined herein.

### *Drawings*

The drawings are objected to because Figure 10A appears to have been omitted. Figures 10B-10I should be labelled 10A-10H, respectively, and the Brief Description of the Drawings should be amended accordingly. Applicant may not request that any objection to the drawings be held in abeyance. See 37 CFR 1.85(a).

### *Claim Objections*

Claims 21 and 24 are objected to because of the following informalities: both claims depend from a non-elected claim.

### *Double Patenting*

Applicant is advised that should claim 21 be found allowable, claim 24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 21 and 24 cover the identical scope.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Written Description*

Claims 1, 3, 6, 21, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The chaperone, nucleic acid, or non-protein, non-nucleic acid compound to be administered to a mammal is an essential element of the claimed invention. However, the specification only describes a single species of therapeutic compound, namely HDJ-2/HSDJ, that could be used in the claimed methods. The specification does not describe any compound that could be used in practicing the method of the invention for treatment of Alzheimer's disease, Parkinson's disease, prion diseases, or any other neurodegenerative disease other than SCA1. In the absence of a written description of the therapeutic compounds, the claimed methods lack written description for the complete genus because the therapeutic compound is an essential element of the claimed method. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, no compounds other than HDJ-2/HSDJ are described. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, no particular identifying characteristics are described for other therapeutic compounds. For example, the specification does not provide a written description of a chaperone that would be effective in the treatment of Alzheimer's disease or Parkinson's disease. Thus, the specification does not describe the genus of therapeutic compounds to be used in the claimed methods. This limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the genus of therapeutic compounds for use in the claimed methods. Thus, it is

concluded that the written description requirement is not satisfied for methods of using the genus of compounds recited in the claims.

### ***Enablement***

Claims 1, 3, 6, 21, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

**Nature of the Invention and Scope of the Claims.** The claims are drawn to a method of treating neurodegenerative disease in a mammal. Claims 1 and 3 are directed to introducing a therapeutically effective amount of a chaperone into the neurological system of a mammal. Claim 6 is directed to introducing a therapeutically effective amount of a compound that increases the effective concentration of a chaperone in the neurological system of a mammal. Claims 21, 24, and 25 are directed to introducing a therapeutically effective amount of a compound which suppresses ataxin-1 aggregation into the neurological system of a mammal. The claims encompass protein therapy, gene therapy, and non-protein, non-nucleic acid compound therapy. Thus, the claims are very broad in scope with regard to the type of compound to be administered.

The claims are very broad in scope with regard to the type of disease to be treated. The claims cover a wide variety of neurodegenerative diseases. As examples, the specification specifically mentions Alzheimer disease, Parkinson disease, the prion disorders, Huntington disease, dentatorubralpallidoluysian atrophy (DRPLA), and spinocerebellar ataxia type 1 and 3 (SCA1 and SCA3) (page 1, lines 15-20).

Furthermore, the claims are very broad in scope with regard to the type of therapeutic effect to be achieved by the method.

**Amount of direction or guidance presented and the presence or absence of working examples.** Example 5 of the specification reveals that ataxin-1 aggregates in SCA1 patients and a transgenic mouse model of ataxia are positive for HDJ-2/HSDJ (pages 20-21). The specification also discloses that ataxin-1 aggregation is suppressed following overexpression of HDJ-2/HSDJ in HeLa cells. The specification does not include any working examples of the claimed invention. Although the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation, it is a factor to be considered, especially in a case involving an unpredictable art such as the therapeutic arts. See MPEP 2164.02.

With regard to gene therapy the specification provides only limited and general guidance at page 5, lines 3-6 and page 14, lines 18-22. The teaching provided in the specification only states that the introducing step of the chaperone can be by gene therapy and that gene therapy modes of introduction can be used to target the introduction of the compound. The specification fails to provide any specific guidance on the generation of the nucleic acid construct to be used in the gene therapy method, on the delivery methods of the nucleic acid, and on the targeting of neurological tissue.

**State of the prior art and predictability of the art.** At the time the invention was made, successful implementation of gene therapy protocols was not routinely achievable by those skilled in the

art. This is reflected in two reviews published around the priority date of this application. Verma et al. (1997) discloses that “there is still no single outcome that we can point to as a success story” (page 239, column 1). The authors go on to state “[t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression” (page 239, column 3). Anderson (1998) states that “there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease” (page 25, column 1) and concludes that “[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered” (page 30). The instant specification fails to provide guidance to the skilled artisan on the parameters for gene delivery for the breadth of the claimed invention. Numerous factors complicate the gene delivery art which cannot be overcome by routine experimentation. These include the fate of the DNA vector itself (volume of distribution, rate of clearance in the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the amount and stability of the protein produced, and the protein’s compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. Hodgson (1995) discusses the drawbacks of viral transduction and chemical transfection methods and states that “[d]eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward” (pages 459-460). Miller et al. (1995) also review the types of vectors available for *in vivo* gene delivery and conclude that “for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems” (page 198, column 1). In the instant application, the specification provides no teachings on the generation of the nucleic acid construct to be used in a gene therapy method, one the

delivery method for the nucleic acid, nor on the targeting of neurological tissue. In the absence of specific guidance, the skilled artisan would have been required to develop successful protocols for practicing the claimed methods, without guidance on a starting point or the direction in which experimentation should proceed. However, given that the gene therapy art was considered highly unpredictable and undeveloped, the skilled artisan would have been required to engage in undue experimentation to come up with successful gene therapy protocols.

The claims encompass a wide variety of neurodegenerative diseases. Price et al. (1998) teaches that the “neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine” (abstract). The specification teaches that the term “neurodegenerative disorders” refers to those disorders which have the characteristic of insoluble aggregates in the cells of the nervous system (page 10, lines 9-12). However, not all neurodegenerative diseases or disorders have the histological characteristic of insoluble aggregates in the cells of the nervous system. See Kumar et al. at pages 725-729. The specification does not teach how a therapeutic effect would be achieved in a patient with a neurodegenerative disease or disorder that is not characterized by the deposition of insoluble protein aggregates in the neural tissue.

The claims encompass a wide variety of chaperones. However, given that the gene therapy art is highly unpredictable and further given that the specification fails to provide specific guidance on which nucleic acids encoding which chaperone can be used to treat a specific neurodegenerative disease of interest, the skilled artisan would have been required to engage in undue experimentation to develop a method within the scope of the claims for treating any particular neurodegenerative disease.

In an article published after the effective filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, “[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be

demonstrated yet in most of the trials conducted so far ... " (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pp. 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of vector types to treat a wide variety of neurodegenerative diseases. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation.

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al., p. 1789, column 1, paragraph 1). Rather, the prior art shows that intensive investigation has met with limited success.

With regard to protein therapy and non-protein, non-nucleic acid compound therapy, the art emphasizes the difficulty associated with developing successful treatment protocols. As discussed above, Price et al. (1998) teaches that the "neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine" (abstract) and Kumar et al. (1992) discloses that "[u]nlike other categories of disease such as infections or trauma that may share etiological origins, the degenerative diseases are unified only by some general clinicopathologic features. Currently, almost all are of obscure origin, and there is no compelling reason

to suppose that they have the same, or even a similar type of cause" (pages 725-726). A wide variety of therapeutic strategies for the treatment of neurodegenerative diseases are being pursued. However, despite intensive effort on the research front, the existence of successful treatment protocols was extremely limited in 1998.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts hold that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Claims 21, 24, and 25 are reach-through claims. The specification fails to disclose any particular structure for the full scope of the compounds recited in the claims, other than HDJ-2/HSDJ as noted above. The specification does not provide any guidance or working examples in this unpredictable art, and thus the artisan would have been unable to prepare the full scope of compounds recited in the claims. Furthermore, an assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product. These claims fail to meet the enablement requirement for the "how to make" prong of 35 U.S.C. 112, first paragraph.

Given the limited examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon *in vivo* administration of a compound as recited in the claims, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon administration

of a compound as recited in the claims, undue experimentation would have been required for one skilled in the art to develop a protocol within the scope of the claims for treating a wide variety of neurodegenerative diseases.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by WO97/43649 (Weiss et al., 1997).

Weiss et al. describes the administration of a chaperone, particularly Hsp60, for the treatment of transmissible spongiform encephalopathy (page 9, paragraphs 4 and 5). Although the reference does not disclose the specific treatment effect, the instant specification provides no more guidance than the prior art.

Thus, the claimed invention is disclosed in the prior art.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

*Anne-Marie Falk*  
ANNE-MARIE FALK, PH.D.  
PRIMARY EXAMINER